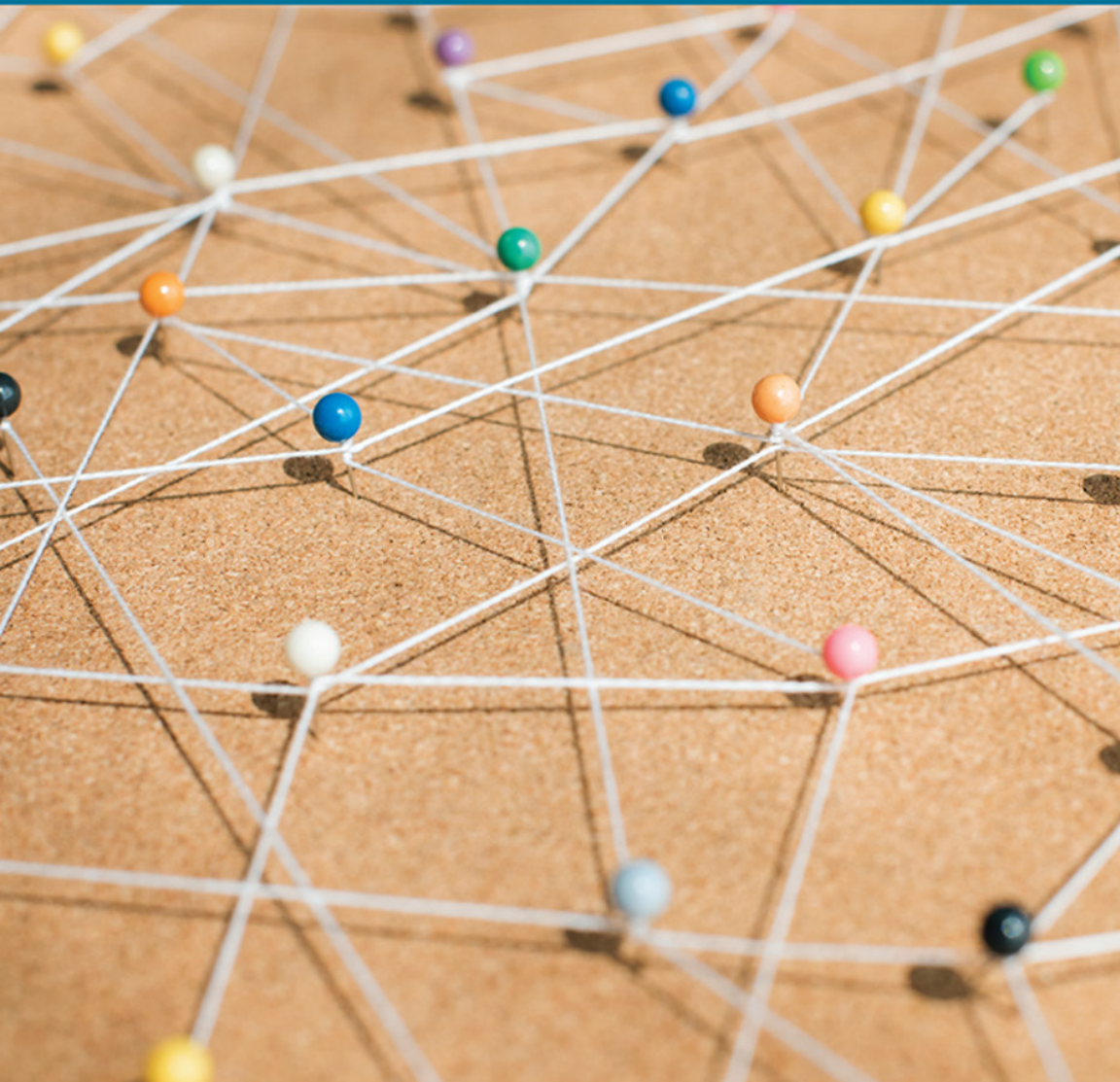
Posttraumatic Stress and Substance Use Disorders

A Comprehensive Clinical Handbook

Edited by Anka A. Vujanovic and Sudie E. Back



Posttraumatic Stress and Substance Use Disorders

Posttraumatic Stress and Substance Use Disorders summarizes the state of the field from a biopsychosocial perspective, addressing key domains of interest to clinicians, students, instructors, and researchers. This book is a valuable resource and reference guide for multidisciplinary practitioners and scientists interested in the evidence-based assessment and treatment of posttraumatic stress and substance use disorders. Chapters written by leaders in the field cover the latest research on assessment, diagnosis, evidence-based treatments, future directions, and much more.

Anka A. Vujanovic, PhD, is a licensed clinical psychologist, an associate professor in the Department of Psychology, and director of the Trauma and Stress Studies Center at the University of Houston.

Sudie E. Back, PhD, is a licensed clinical psychologist, a professor in the Department of Psychiatry and Behavioral Sciences, and director of the Drug Abuse Research Training (DART) program at the Medical University of South Carolina.

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To Mila and Stella, for filling our days with love, wonder, joy, and laughter.

Anka A. Vujanovic

To Steve for his unwavering love and support, and to Liam for his hugs and laughter. I treasure you both deeply.

Sudie E. Back

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Contributors

Zachary W. Adams, PhD, Indiana University School of Medicine

Ananda B. Amstadter, PhD, Virginia Commonwealth University

Isabel F. Augur, BS, University of Arkansas

Sudie E. Back, PhD, Medical University of South Carolina and Ralph H. Johnson VA Medical Center

Emma L. Barrett, PhD, University of New South Wales

Erin C. Berenz, PhD, University of Illinois at Chicago

Christopher R. Berghoff, PhD, University of South Dakota

Kathleen T. Brady, MD, PhD, Medical University of South Carolina and Ralph H. Johnson VA Medical Center

Leslie A. Brick, PhD, Bradley/Hasbro Children's Research Center of Rhode Island Hospital and Alpert Medical School of Brown University

Delisa Brown, PhD, Howard University and Medical University of South Carolina

Christy Capone, PhD, Alpert Medical School of Brown University and Providence VA Medical Center

Lisa R. Cohen, PhD, Columbia University

Carla Kmett Danielson, PhD, Medical University of South Carolina

Brittany C. Davis, PhD, VA San Diego Healthcare System and University of California, San Diego School of Medicine

Mark Deady, PhD, University of New South Wales

Sunny J. Dutra, PhD, National Center for PTSD, Behavioral Science Division, VA Boston Healthcare System and Boston University School of Medicine

Emily R. Dworkin, PhD, University of Washington School of Medicine

Faith Erickson, BS, University of California, San Diego School of Medicine

Julianne C. Flanagan, PhD, Medical University of South Carolina

Daniel F. Gros, PhD, Medical University of South Carolina and Ralph H. Johnson VA Medical Center

Moira Haller, PhD, VA San Diego Healthcare System and University of California, San Diego School of Medicine

Jessica Hamblen, PhD, National Center for PTSD, Geisel School of Medicine at Dartmouth

Rochelle Hanson, PhD, Medical University of South Carolina

Aisling V. Henschel, MS, University of Missouri-Kansas City

Denise Hien, PhD, Rutgers, The State University of New Jersey

Stephanie M. Jeffirs, BS, Medical University of South Carolina

Kevin P. Jensen, PhD, VA Connecticut Healthcare System and Yale University School of Medicine

Tiffany Jenzer, MA, State University of New York, University at Buffalo

Matt R. Judah, PhD, Old Dominion University

Lorig K. Kachadourian, PhD, National Center for PTSD, VA Connecticut Healthcare System and Yale University School of Medicine

Debra Kaysen, PhD, University of Washington School of Medicine

Ivans Kihas, BA, University of New South Wales

Therese Killeen, PhD, RN, Medical University of South Carolina

Cynthia L. Lancaster, PhD, University of Nevada, Reno

Keren Lehavot, PhD, VA Puget Sound Health Care System and University of Washington School of Medicine

Lisa Litt, PhD, Icahn School of Medicine at Mount Sinai

Robert Lyons, BA, VA San Diego Healthcare System and San Diego State University/ University of California, San Diego School of Medicine

Brian P. Marx, PhD, National Center for PTSD, Behavioral Science Division, VA Boston Healthcare System and Boston University School of Medicine

Mark P. McGovern, PhD, Stanford University School of Medicine

Sage McNett, BS, University of Illinois at Chicago

Katherine L. Mills, PhD, University of New South Wales

Sonya B. Norman, PhD, VA Center of Excellence for Stress and Mental Health and National Center for PTSD, VA San Diego Healthcare System and University of California, San Diego School of Medicine

Elizabeth Nosen, PhD, G.V. (Sonny) Montgomery VA Medical Center

Nicole R. Nugent, PhD, Bradley/Hasbro Children's Research Center of Rhode Island Hospital and Alpert Medical School of Brown University

Katherine Paltell, BA, University of Illinois at Chicago

Ismene Petrakis, MD, VA Connecticut Healthcare System and Yale University School of Medicine

Jennifer P. Read, PhD, State University of New York, University at Buffalo

Lauren Rodriguez, MA, State University of New York, University at Buffalo

Elizabeth C. Saunders, MS, Dartmouth Institute for Health Policy and Clinical Practice

John Sevcik, MSW, VA San Diego Healthcare System

Christina M. Sheerin, PhD, Virginia Commonwealth University

Tracy L. Simpson, PhD, VA Puget South Health Care System and University of Washington School of Medicine

Mehmet Sofuoglu, MD, PhD, VA Connecticut Healthcare System and Yale University School of Medicine

Iris Torchalla, PhD, R.Psych, University of British Columbia, Centre for Health Evaluation and Outcome Sciences (CHÉOS)

Matthew T. Tull, PhD, University of Toledo

Anka A. Vujanovic, PhD, University of Houston

Kevin Washington, PhD, Grambling State University

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In that spirit, we devote this project to those struggling with posttraumatic stress and substance use, with the hope that this volume will advance discourse, science, and practice, and in so doing, ultimately lead to long-term healing and recovery.

Part I
Overview

1

PTSD and Substance Use Disorders

A Clinical Overview

Anka A. Vujanovic and Sudie E. Back

Overview

Posttraumatic stress disorder (PTSD) and substance use disorders (SUD) are complex psychiatric conditions that commonly co-occur (McCauley, Killeen, Gros, Brady, & Back, 2012), presenting a significant challenge to clinical scientists and practitioners. The development of a deeper understanding of this comorbidity is critical, as the co-occurrence of PTSD and SUD presents a clinical and public health concern. The comorbidity is challenging, difficult to treat, and marked by a more costly and chronic clinical course when compared to either disorder alone (McCauley et al., 2012; Mills Teesson, Ross, & Peters, 2006; Schäfer & Najavits, 2007). Individuals with PTSD/SUD comorbidity, relative to those with either disorder alone, tend to manifest worse treatment adherence, less improvement in symptomatology during treatment, more legal problems, increased risk for experiencing violence, poorer social functioning, more severe physical health problems, and higher rates of suicide attempts (Foa & Williams, 2010; McCauley et al., 2012). Moreover, PTSD, including subclinical PTSD (Norman, Tate, Anderson, & Brown, 2007), is associated with strong drug cravings (Coffey et al., 2002; Saladin et al., 2003) and withdrawal symptoms (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013), as well as a greater tendency to use substances to alleviate negative mood states (Back, Brady, Jaanimägi, & Jackson, 2006; Chilcoat & Breslau, 1998; Jacobsen, Southwick, & Kosten, 2001).

The goal of this volume, therefore, is to provide an up-to-date clinical resource for clinicians, students, teachers, and researchers interested in learning more about PTSD/SUD comorbidity. This book reviews clinically relevant literature on PTSD/SUD and provides a consolidated summary of our current understanding of etiological pathways, phenomenology, and clinical correlates, as well as "best practice" avenues for assessment and treatment. This first chapter aims to: (1) briefly review

the prevalence of trauma and PTSD among SUD populations, and the prevalence of substance use and SUD among individuals who have experienced trauma or have PTSD; (2) summarize common past clinical practices for PTSD/SUD populations; (3) highlight current evidence-based trends and promising clinical avenues; and (4) delineate roads for future clinical and empirical exploration.

Prevalence Rates

The majority of the general population will experience a traumatic life event (e.g., natural disaster, motor vehicle accident, sexual assault), as defined by the *DSM-5* (Kilpatrick et al., 2013), and approximately 6–8% of the general population will develop PTSD at some point during their lifetime. Notably, subclinical PTSD and clinical (i.e., diagnostic) PTSD are associated with similar rates of comorbidity and functional impairment (Pietrzak, Goldstein, Southwick, & Grant, 2011), underscoring the clinical significance of considering subclinical PTSD in conversations about PTSD/SUD (McLaughlin et al., 2015; Ruglass et al., 2017). Among individuals with PTSD, the prevalence of co-occurring SUD, including alcohol use disorder (AUD), is estimated to be as high as 52%, substantially higher than the prevalence of lifetime SUD in the general population, which is approximately 35% (Kessler, Chiu, Demler, & Walters, 2005; Mills et al., 2006; Pietrzak et al., 2011).

Among adults with SUD, rates of trauma exposure are as high as 95% (Dansky, Saladin, Brady, Kilpatrick, & Resnick, 1995; Reynolds et al., 2005), depending on the sample and substance class studied. Among individuals with SUD, the prevalence of lifetime PTSD is estimated to be between 26% and 60%, while the prevalence of current PTSD is estimated to be 15–42% (Back et al., 2000; Brady, Back, & Coffey, 2004; Dragan & Lis-Turlejska, 2007; Driessen et al., 2008; Jacobsen et al., 2001; Mills et al., 2006; Reynolds, Hinchliffe, Asamoah, & Kouimtsidis, 2011; Reynolds et al., 2005; Schäfer et al., 2010).

Notably, the aforementioned prevalence rates are significantly higher among treatment-seeking populations (McCauley et al., 2012). The considerable range in published prevalence rates is largely due to variability across populations, clinical settings, and measures employed to assess PTSD and SUD. Relatedly, changes in diagnostic criteria for PTSD and SUD (Henschel, Jeffirs, Augur, & Flanagan, this volume) may influence changes in prevalence rates over time. Taken together, approximately one in every two individuals with PTSD *or* SUD will meet criteria for the other disorder. Thus, PTSD/SUD represents a meaningful and common comorbidity that is frequently encountered in clinical settings.

Historical Review of PTSD/SUD Treatment

Several clinical models of care for PTSD/SUD have been adopted at different points in history. Until relatively recently, the most common treatment model employed across settings was the *sequential model* of care, which posits that the SUD needs to be treated first and trauma-focused interventions should be deferred until sustained abstinence, as defined by the clinical provider or treatment setting, from substance use

is achieved. In the sequential model, interventions for SUD and PTSD were typically provided by different clinicians, usually across separate treatment clinics or agencies. Despite little empirical support, the sequential model continues to be maintained in practice by several factors. First, some clinicians may be concerned that continued substance use during PTSD treatment will interfere with the cognitive or emotional processing of the trauma, resulting in little or no reduction in PTSD severity. Second, others purport that engaging in PTSD treatment will serve to maintain or increase ongoing substance use, or lead to relapse following abstinence due to insufficient or compromised emotion regulation skills (Souza & Spates, 2008). Third, clinical providers are often trained either in the assessment and treatment of PTSD *or* SUD but rarely both. Thus, preference for the sequential model may be driven by pragmatic issues, such as insufficient training or limited familiarity with comorbid populations. Relatedly, many clinical settings specialize in the treatment of PTSD or SUD, and thus, services may not be available for the treatment of the co-occurring condition. Finally, clinical awareness of the prevalence and complexity of PTSD/SUD comorbidity has been a relatively recent development within the past 20 years. With greater awareness and empirical scrutiny came the realization that individuals with PTSD/SUD are at increased risk for relapse to substance use for as long as the PTSD remains untreated (e.g., McCauley et al., 2012).

Concurrent and *integrated* models of care emerged as a result of the challenges inherent in the sequential model, including high relapse rates and limited care coordination between providers. Concurrent models of care generally offer treatment for PTSD and SUD at the same time by different clinicians. For example, a client may be in individual PTSD treatment with one provider and in SUD treatment with another at the same time. As another example, individuals in residential treatment for SUD may be offered weekly PTSD treatment in the form of individual or group therapy. *Integrated* models of care underscore the importance of the intersection of PTSD and SUD and thus indicate the treatment of both disorders simultaneously by the same clinician. This model of care is informed largely by the self-medication theory (Khantzian, 1999; Reed, Anthony, & Breslau, 2007), which purports that substance use is driven in part by an attempt to ameliorate (i.e., "medicate") symptoms of PTSD. According to the integrated model, providing psychoeducation regarding the interplay of PTSD/SUD and targeting PTSD symptoms alongside SUD may improve long-term outcomes.

The majority of individuals with PTSD/SUD continue to only receive SUD treatment (Najavits, Sullivan, Schmitz, Weiss, & Lee, 2004; Young, Rosen, & Finney, 2005), contrary to most clients' preferences (Back, Brady, Jackson, Salstrom, & Zinzow, 2005; Brown, Stout, & Gannon-Rowley, 1998; Brown et al., 1998). Adults in treatment for SUD are often not assessed for PTSD and not offered trauma-informed interventions, and vice versa (Bujarski et al., 2016; Mills et al., 2006; Reynolds et al., 2005). Therefore, this volume offers a review of evidence-based assessment approaches for PTSD in the context of SUD (Dutra & Marx, this volume) as well as assessment of SUD in individuals with PTSD symptoms (Barrett, Deady, Kihas, & Mills, this volume). More well-constructed bridges between science and practice are thus imperative in order to deliver and implement evidence-based practices. In addition, greater

attention to innovative dissemination and implementation efforts (Dworkin, Lehavot, Simpson, & Kaysen, this volume) is imperative to increase the reach of the "treatments that work" to ethnically diverse and underserved communities, including rural, low-income, non-English-speaking, and inner-city populations. Given the diversity of American society, it is important also to consider applying a cultural lens to PTSD/SUD treatment and to adapt extant evidence-based interventions for cultural subgroups and/or to develop novel specialized interventions for specific populations (Washington & Brown, this volume).

Perhaps most importantly, despite the scientific and clinical strides of the past 20 years, there continues to be no consensus regarding "best practice guidelines," and most treatment-seeking individuals with PTSD/SUD are passed between PTSD and SUD treatment services with little care coordination (Roberts, Roberts, Jones, & Bisson, 2015). Recent systematic reviews and meta-analyses (Roberts et al., 2015; Simpson, Lehavot, & Petrakis, 2017) have found that interventions that integrate exposure-based PTSD treatment with behavioral SUD treatment are recommended, but that there are perhaps "no wrong doors" (Simpson et al., 2017). That is, individuals with PTSD/SUD may benefit from a variety of treatment options, including standard SUD treatment.

Current Treatment Trends

Several evidence-based PTSD/SUD interventions are currently available. Leading interventions are profiled in this volume and include cognitive-behavioral individual or group-based approaches as well as pharmacotherapies. Seeking Safety presents the most well-studied and widely disseminated PTSD/SUD intervention (Litt, Cohen, & Hien, this volume). Emerging evidence-based PTSD/SUD interventions for adults with considerable promise also include (a) Concurrent Treatment of PTSD and SUD using Prolonged Exposure (COPE; Back, Killeen, & Brady, this volume), which integrates prolonged exposure therapy for PTSD with cognitive-behavioral therapy for SUD; and (b) Integrated Cognitive-Behavioral Therapy for PTSD and SUD (ICBT; Saunders, McGovern, Capone, & Hamblen, this volume), which presents a cognitive-behavioral, skills-based approach. Both COPE and ICBT are intended to be delivered in individual formats, while Seeking Safety may be an individual or group-based intervention. In clinical practice, pharmacotherapies for PTSD/SUD are popular and may be offered as stand-alone interventions or as adjunctive interventions to cognitive-behavioral therapies (Kachadourian, Jensen, Sofuoglu, & Petrakis, this volume). Notably, fewer evidence-based intervention options are available for adolescents, but a leading intervention in this domain is Risk Reduction Through Family Therapy (Danielson, Adams, & Hanson, this volume).

Alongside established interventions, promising intervention avenues worthy of increased empirical and clinical attention include third-wave behavioral therapies (Berghoff & Tull, this volume) and transdiagnostic treatments (Judah, Lancaster, & Gros, this volume). Adaptations of evidence-based interventions to inpatient settings are also a topic of great clinical relevance and concern, since more severe PTSD and/or SUD is often encountered and treated in residential contexts (Haller et al., this volume).

Across clinical trials and clinical practice, PTSD/SUD populations tend to manifest high rates of treatment drop-out and low treatment adherence; and treatment effects leave significant room for improvement (Roberts et al., 2015). The high levels of avoidance, distress, and functional impairment inherent in PTSD/SUD populations (e.g., Miles, Smith, Maieritsch, & Ahearn, 2015; Szafranski, Gros, Menefee, Wanner, & Norton, 2014) often present significant barriers to treatment and highlight challenges to existing clinical practices, even those that are scientifically informed. In summary, there is substantial room for improvement and progress, and future directions that are culturally sensitive and that adapt a biopsychosocial perspective will be necessary to address this difficult-to-treat clinical presentation.

Future Directions

As discussed in each of the forthcoming chapters, substantive additional research is needed to advance a clinically meaningful understanding of PTSD/SUD comorbidity and further our progression toward developing optimal treatments. While increasing work is focused upon innovatively examining PTSD/SUD relations using rigorous scientific approaches, the extant literature contains considerable gaps with significant room for growth. Specifically, the PTSD/SUD literature may benefit from more longitudinal and experimental studies to improve our understanding of the naturalistic temporal relations of PTSD and SUD (Berenz, McNett, & Paltell, this volume). More long-term treatment outcome studies following diverse types of interventions across various clinical settings are also needed. With improved knowledge of the physical, psychological, and functional outcomes of PTSD/SUD (Rodriguez, Jenzer, & Read, this volume) and relevant modifiable biological, cognitive-affective, and behavioral mechanisms, we will be able to refine and build upon leading evidence-based interventions and develop novel interventions. Finally, there may be clinical utility in developing novel, integrated, cognitive-behavioral interventions for PTSD/SUD to offer greater choices of effective treatment options. For example, integrating cognitive processing therapy for PTSD (Resick, Nishith, Weaver, Astin, & Feuer, 2002) with cognitive-behavioral therapy for SUD may offer a promising treatment avenue (Vujanovic, Smith, Green, Lane, & Schmitz, 2018). Sequential, multiple assignment, randomized trials may also be necessary in order to better understand how we might use evidence-based principles to tailor PTSD/SUD treatment to the individual (Schmitz et al., 2018).

In conjunction with testing extant interventions among various populations and developing novel interventions based upon an integration of evidence-based treatments for PTSD and SUD, a more basic scientific lens is necessary to inform our biopsychosocial perspectives of this complex comorbidity. The genetic/epigenetic underpinnings of PTSD/SUD ultimately will illuminate etiological and maintenance pathways, thus informing prevention and intervention efforts (Sheerin, Brick, Nugent, & Amstadter, this volume). Cultivating our understanding of substance use motives, help-seeking attitudes, and treatment engagement and completion among various PTSD/SUD populations will enhance our ability to intervene meaningfully to foster long-term recovery. A better understanding of gender similarities and

differences relevant to the prevalence, etiology, maintenance, and treatment outcomes of PTSD/SUD is an area worthy of greater scientific attention (Torchalla & Nosen, this volume). Finally, studies among adolescents and adults, civilian and veteran populations, and socioeconomically and racially diverse individuals struggling with misuse of various substance classes are imperative (Washington & Brown, this volume). Unanswered questions and unexplored topics abound among both clinicians and researchers, students and teachers. To bridge the lengthy gap between PTSD/SUD science and practice, clinicians and researchers ideally should work together to ensure that science is continually informed by the challenges and triumphs of clinical care, and that clinical practice is based upon the most recent scientific advances. Ultimately, a multidisciplinary, team-based approach will be what is required to ameliorate the immeasurable suffering and burden endured by so many affected by PTSD and SUD.

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2

Development of Comorbid PTSD and Substance Use Disorders

Erin C. Berenz, Sage McNett and Katherine Paltell

Introduction

The first chapter of this book by Vujanovic and Back clearly outlines the public health relevance of co-occurring posttraumatic stress disorder (PTSD) and substance use disorders (SUD), including the challenges that clinicians and health workers face when addressing the treatment needs of this population. In order to best address these treatment challenges, we must understand the etiological and maintenance factors contributing to the onset of comorbid PTSD/SUD. This chapter aims to review the predominant etiological models for PTSD/SUD and is written with several key assumptions in mind. The first is that the proposed theoretical explanations for PTSD/SUD etiology are not mutually exclusive. Rather, we have the task of synthesizing the available data from a variety of methodological perspectives to inform a complex picture of the numerous and varied influences on PTSD/SUD development. This chapter will review evidence for explanatory models of PTSD/SUD, with the understanding that there is no single best model, but complementary explanations across multiple models. It may be the case that individuals experience risk from each of the described sources, and it may be that different models are more relevant for certain individuals. The second assumption is that not all explanations of PTSD/SUD comorbidity assume causal associations between these disorders. Our framework for understanding PTSD/SUD etiology must accommodate the evidence that a proportion of the covariation between these disorders is explained by common factors, as described below. By increasing our awareness and understanding of the heterogeneity of etiologies underlying PTSD/SUD, we will be better positioned to identify multiple prevention and intervention targets at different points over the course of development.

Briefly, the primary etiological models of risk for PTSD/SUD reviewed in this chapter are (1) the *shared liability model*; and two categories of causal models: (2) the

self-medication model, by which trauma and/or PTSD are thought to be causally related to the onset of substance use and/or SUD, and (3) *susceptibility models*, whereby substance use and/or SUD are presumed to be causally related to an individual's likelihood to experience trauma and/or develop PTSD following trauma exposure. This chapter will summarize key evidence for each of these models and will conclude with a summary of the state of the literature and suggestions for future research efforts.

Shared Liability Model

The shared liability model suggests that PTSD and SUD frequently co-occur due to common familial risk (i.e., genetic factors and shared environmental influences underlying both disorders; Krueger & Markon, 2006). The strongest support for this model is derived from twin studies, which estimate the proportion of variance within a population that can be attributed to genetic factors, shared environmental influences, and non-shared environmental influences. Further, twin studies are able to estimate the proportion of variance from each of these sources that is unique to versus shared across two or more phenotypes (for a review of twin study methods, see Kendler & Prescott, 2006).

A number of twin studies have documented significant genetic and shared environmental influences on trauma and substance use phenotypes. For example, familial risk explains significant variance in interpersonal stressful events and traumatic event exposure (e.g., sexual or physical assault; Kendler, Karkowski, & Prescott, 1999). In other words, the tendency to experience interpersonal stressors, including interpersonal traumatic events, runs in families, in part due to genetic factors. The specific characteristics that account for this heritability are not well understood, although it has been shown that the genetic risk underlying propensity for interpersonal stress overlaps with that for trait-level neuroticism (Kendler, Gardner, & Prescott, 2003). It is important to note that the moderate heritability of interpersonal trauma exposure does not mean that individuals are responsible for their experiences of trauma. It is possible, for example, that perpetrators of violence target individuals on the basis of certain traits that may be heritable. Twin studies have further estimated that approximately 30–40% of variance in PTSD is accounted for by genetic factors (Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993), with a portion of the genetic liability overlapping with that for trauma exposure, but a majority being unique to PTSD (Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2012).

Substance use phenotypes (e.g., age of initiation of use, quantity/frequency of use) have generally demonstrated higher heritability rates compared to trauma and PTSD phenotypes. However, the available literature indicates that developmental stage is extremely important for understanding the role of shared environment versus genetic factors. For example, phenotypes observed earlier in the developmental trajectory (e.g., adolescence), such as substance use initiation, tend to be more strongly influenced by shared environmental factors (e.g., peer influences) compared to genetic factors, whereas progression to SUD tends to be more influenced by genetic factors, with the role of shared environment decreasing (e.g., Fowler et al., 2007). In fact, SUD has been found to be largely determined by genetic factors, more so than PTSD,

with heritability estimates of 40–60% being documented in the literature (Agrawal & Lynskey, 2008; Knopik et al., 2004). Although there are common genetic factors underlying multiple types of SUD (Young, Rhee, Stallings, Corley, & Hewitt, 2006), a significant portion of genetic risk for substance use and SUD also appears to be substance-specific (Sartor et al., 2010); in other words, one individual could have elevated genetic risk for alcohol use disorder (AUD), whereas another individual could have elevated genetic risk for cannabis use disorder. Similarly, although a portion of familial risk is unique to PTSD and SUD, respectively, overlapping variances across PTSD and SUD phenotypes have also been found.

Overlap in Genetic Risk for Trauma Exposure and Substance Use Phenotypes

McLeod and colleagues (2001) examined genetic overlap for combat exposure and alcohol consumption in a sample of 4,072 male Veteran twin pairs from the Vietnam Era Twin (VET) Registry and found that genes that influence the degree of combat exposure also influence the level of alcohol consumption ($r = 0.21$). Other work from the VET Registry utilized a co-twin control design among monozygotic (MZ) twin pairs to evaluate the influence of combat trauma exposure on *DSM-III-R* alcohol and cannabis dependence (Koenen et al., 2003). Co-twin control designs are unique in that they capitalize on the known genetic and environmental similarities between twins (e.g., MZ twins are assumed to be identical in their genetic make-up and shared environment) to evaluate the likelihood of a clinical outcome (e.g., SUD) for a twin exposed to a particular environment (e.g., combat trauma) compared to a twin not exposed to that environment (e.g., no history of combat trauma). Koenen and colleagues (2003), utilizing an MZ-only co-twin control design, found that combat trauma history significantly predicted alcohol and cannabis dependence, even after accounting for shared genetic and environmental risk, as well as combat-related PTSD. Therefore, although there is evidence for shared genetic risk between trauma exposure and substance use phenotypes, there is also evidence that shared genetic risk does not unilaterally account for the observed associations between these phenotypes.

Overlap in Genetic Risk for PTSD and Substance Use Phenotypes

A number of twin studies have been conducted with respect to PTSD and comorbid SUD, almost all of which utilize the VET Registry data. Interestingly, research in the VET Registry found that PTSD is the only disorder traditionally characterized as an internalizing disorder (e.g., anxiety or mood disorder) that maps onto both a higher-order internalizing factor and an externalizing factor, which includes SUD (Wolf et al., 2010). Such findings indicate that PTSD has a unique relationship with SUD as far as shared liability is concerned, relative to other disorders frequently reported to co-occur with SUD. Also using the VET Registry, Scherrer and colleagues (2008) found that a moderate amount of genetic variance in risk for PTSD overlaps with that for alcohol dependence and nicotine dependence (30% and 20%,

respectively). Contrary to previous findings in the same dataset (reported above; Koenen et al., 2003), they found that combat exposure was not associated with alcohol dependence or nicotine dependence after accounting for genetic and environmental PTSD influences. Xian and colleagues (2000) similarly found evidence in the VET Registry for moderate overlap in genetic and shared environmental risk for PTSD and SUD.

Sartor and colleagues (2011) published the only twin study of PTSD and SUD, to our knowledge, that was conducted in a female sample. Specifically, they utilized a sample of 3,768 female twins (ages 18–29) enrolled in the Missouri Adolescent Female Twin Study to evaluate heritability for PTSD, as well as overlap in genetic influences between PTSD and *DSM-IV* alcohol dependence. They found evidence for higher heritability for PTSD than had been reported previously in male samples (72%), as well as significant overlap in genetic variance for PTSD and alcohol dependence ($r = 0.54$). It is worth noting, however, that the sample size of women with PTSD was low ($N = 138$), which the authors acknowledge may have influenced the results.

Limitations and Future Directions

Twin and family studies are important for estimating sources of variance for psychiatric disorders and provide important information on the nature of psychiatric comorbidity. However, these studies are not able to provide insight into specific factors accounting for such risk. Familial risk for trait-level neuroticism (Holeva & Tarrier, 2001; Parslow, Jorm, & Christensen, 2006; Sintov, Kendler, Walsh, Patterson, & Prescott, 2009) or other characteristics, such as juvenile antisocial behavior (Jang, Stein, Taylor, Asmundson, & Livesley, 2003) may account for some of the shared liability underlying trauma and substance use phenotypes, but additional research is needed to understand the specific factors accounting for this overlap. It is possible that individual difference factors known to correlate with PTSD/SUD also share familial liability with that underlying PTSD/SUD. For example, aspects of emotion regulation, such as expressive suppression, or effort to refrain from expressive emotion, have demonstrated moderate heritability (McRae et al., 2017). A number of emotion regulation measures have demonstrated significant associations with PTSD and SUD phenotypes in a variety of sample types and research designs (e.g., McLean & Foa, 2017; Shadur & Lejuez, 2015). Similarly, anxiety sensitivity, or a fear of anxiety and related sensations, is moderately heritable and evidences meaningful and consistent associations with PTSD and SUD (for a review, see Vujanovic et al., 2018). Unfortunately, given the scope and breadth of most twin studies, few such investigations have the capacity to administer assessments of specific individual difference factors, such as emotion regulation and anxiety sensitivity. Regardless, efforts to evaluate these types of phenotypes in twins at various stages of development would be incredibly informative to our understanding of malleable risk factors that may account for a portion of shared liability in PTSD/SUD. Molecular genetic studies also have the potential to inform these questions, and Chapter 15 of this book provides a review of the state of the PTSD/SUD molecular genetic research.

Another outstanding limitation of twin and family studies to date revolves around the limited availability of diverse data. For instance, a majority of studies utilize the VET Registry, which consists of male twin pairs enrolled in the military during the Vietnam War era (Eisen, True, Goldberg, Henderson, & Robinette, 1987). Male Vietnam veterans represent an idiographic segment of the trauma-exposed population in the United States. Only one twin study of PTSD/SUD to our knowledge (reviewed above) has been conducted in female twins. No twin studies of PTSD/SUD have included male and female twin pairs within the same registry, which precludes an ability to evaluate differences in model fit as a function of sex. In other words, we do not know if the genetic and environmental influences on PTSD and SUD are comparable between men and women. Future twin research incorporating assessments of PTSD and SUD phenotypes in male and female twin pairs would be hugely informative.

Self-Medication Model

The *self-medication hypothesis* presumes that individuals with a history of trauma and/or PTSD are at increased risk for SUD due to repeated use of substances to cope with trauma-related symptoms (Khantzian, 1999); see Figure 2.1. The self-medication hypothesis is largely rooted in operant conditioning theory, in that individuals who use alcohol or other substances to cope with trauma-related negative affect may experience temporary relief of negative affect, which in turn negatively reinforces the use of the substance in other similar affective (e.g., anxiety) and situational (e.g., triggering environments) contexts, ultimately leading to more frequent and maladaptive use. The hypothesis is also rooted in classical conditioning theory, in that as trauma reminders and related symptoms become paired with substance use, these reminders and symptoms become a conditioned stimulus for substance craving. This theoretical model is attractive in that it is intuitive; in fact, clients with comorbid PTSD/SUD often endorse using substances to cope with negative affect (e.g., Waldrop, Back, Verduin, & Brady, 2007b), and they also report that they perceive there to be functional links between their PTSD and SUD (Brown, Stout, & Gannon-Rowley, 1998). Taken together, it is unsurprising that the self-medication model has gained the most theoretical and empirical attention.

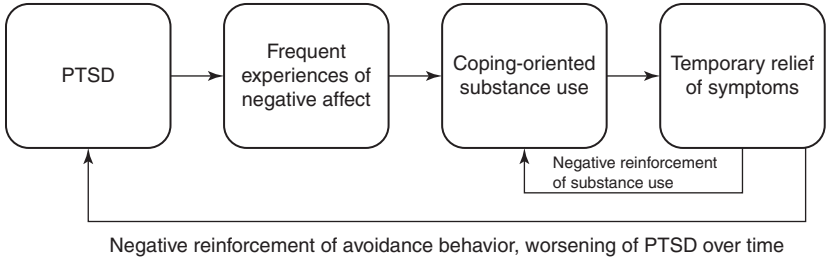

Figure 2.1 Graphic representation of the self-medication model for explaining the etiology of comorbid PTSD and SUD.

Correlational Studies

Several prospective, epidemiological studies have been conducted to examine patterns of association between PTSD and SUD. A strength of epidemiological studies is that they are often able to minimize selection and ascertainment bias (Westreich, 2012). A majority of PTSD/SUD epidemiological studies have determined that PTSD conveys greater risk for SUD than the reverse association. For example, a National Comorbidity Survey study, based upon *DSM-III* diagnostic criteria, examined the timing of individuals' worst lifetime traumatic event and determined that PTSD was the "primary" diagnosis more often than alcohol dependence in individuals with PTSD and alcohol dependence comorbidity (Kessler et al., 1995). Chilcoat and Breslau (1998a) examined patterns of prospective association between PTSD and SUD in approximately 1,000 adults (age range = 21–30) recruited in a community setting. They found significant associations between PTSD and subsequent onset of SUD but not the reverse association; however, a significant limitation of this study was an insufficient number of individuals with baseline SUD. The authors conducted another prospective investigation, in which they detected evidence for associations in both directions, although the effect was stronger for PTSD predicting SUD, as compared to SUD predicting PTSD (Chilcoat & Breslau, 1998b). A longitudinal, community-based study of at-risk adolescents ($N = 627$) also found a significant association between PTSD at time 1 and SUD at time 2 ($OR = 7.29$, 95%CI = 1.18–45.25), yet did not detect evidence for the reverse association (Wolitzky-Taylor, Bobova, Zinbarg, Mineka, & Craske, 2012). Finally, a study of Operation Iraqi Freedom (OIF) National Guard soldiers ($N = 922$) found that PTSD predicted subsequent SUD, but SUD did not predict PTSD (Kline et al., 2014). These studies provide compatible findings in diverse types of trauma-exposed samples; however, causal associations cannot be drawn from these data. Further, the sample sizes of many of these studies are relatively small for epidemiological research, and a number of other studies find conflicting evidence (see Susceptibility Models section).

Numerous cross-sectional and longitudinal studies of PTSD and SUD phenotypes in a variety of samples also provide support for self-medication models of comorbidity. For example, adults with PTSD compared to without PTSD, and with greater compared to lesser PTSD symptom severity, consistently report greater motivation to use alcohol and other substances for coping reasons (Berenz et al., 2016b; Bonn-Miller, Vujanovic, Feldner, Bernstein, & Zvolensky, 2007; Bonn-Miller, Vujanovic, Boden, & Gross, 2011; McDevitt-Murphy, Fields, Monahan, & Bracken, 2015; O'Hare & Sherrer, 2011; Potter, Vujanovic, Marshall-Berenz, Bernstein, & Bonn-Miller, 2011; Waldrop et al., 2007a). Available research in adolescent samples corresponds with this pattern of findings, with PTSD symptoms associated with greater motivation to use cannabis (Bujarski et al., 2012) and alcohol (Dixon, Leen-Feldner, Ham, Feldner, & Lewis, 2009). Support for a mediating role for coping motives in the association between PTSD symptoms and alcohol consumption and problems has also been documented (Kaysen et al., 2007; Ullman et al., 2013; Yeater et al., 2010).

Longitudinal research from our group and others has documented associations between trauma exposure and/or PTSD and subsequent increases in alcohol

consumption. For example, we found that in a sample of emerging adults, new incidents of interpersonal trauma exposure (e.g., sexual or physical assault) predicted subsequent increases in alcohol consumption, above and beyond a prior history of trauma and prior levels of alcohol use (Berenz et al., 2016a). Read and colleagues documented evidence for bidirectional associations between PTSD symptoms and coping-oriented alcohol use in a college sample, with PTSD symptom severity and coping motives for alcohol use each predicting worse alcohol-related consequences (Read, Griffin, Wardell, & Ouimette, 2014). An investigation using the National Women's Study also found support for an association between a new assault and increases in drug and alcohol use (Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997). Kaysen and colleagues similarly documented associations between incapacitated rape (i.e., sexual assault while intoxicated) and subsequent increases in alcohol use (Kaysen, Neighbors, Martell, Fossos, & Larimer, 2006). Studies in treatment settings also support links between PTSD symptoms and substance use phenotypes. For example, an investigation of weekly changes in symptoms found that changes in PTSD symptoms predicted next-week changes in opiate dependence symptoms (Ouimette, Read, Wade, & Tirone, 2010).

Ecological Momentary Assessment (EMA) studies have been particularly useful for evaluating acute fluctuations in PTSD symptoms and substance use, and have provided additional evidence for the self-medication model. For example, Simpson and colleagues (2007) collected data on daily patterns of PTSD symptoms and alcohol use and found that increases in daily PTSD symptoms predicted subsequent increases in alcohol consumption for adults endorsing higher compared to lower coping motives for alcohol use. Buckner and colleagues (2018) evaluated associations between various PTSD symptom clusters and patterns of cannabis use in a sample of 87 adults and found that hyperarousal PTSD symptoms uniquely predicted increased cannabis use over a two-week period, followed by temporary reductions in self-reported state anxiety symptoms. Additional EMA studies over varying lengths of time, incorporating diverse phenotypes and profiles (e.g., polysubstance use), may be particularly useful for furthering our understanding of acute interrelations between PTSD and substance use.

Clinical Laboratory Designs

Human laboratory studies have provided particularly convincing support for the self-medication model, particularly with respect to individuals with comorbid PTSD and AUD. Coffey and colleagues conducted a series of studies among treatment-seeking individuals with PTSD/AUD utilizing a trauma and alcohol cue reactivity paradigm (Coffey et al., 2002, 2006). This paradigm is an adaptation of classic alcohol and drug cue reactivity studies (e.g., Monti et al., 1987), in which participants are presented with four combinations of cues, consisting of a narrative cue (i.e., personalized trauma narrative or standard neutral narrative) followed by an *in vivo* beverage cue (i.e., individualized alcoholic beverage of choice or water). Physiological (i.e., salivation) and subjective measures of craving are evaluated within and between participants to evaluate patterns of cue response to each of the four possible cue

combinations (trauma–alcohol, trauma–neutral, neutral–alcohol, neutral–neutral). The findings show that individuals with comorbid PTSD/AUD exhibit craving and salivation in response to trauma cues, even in the absence of alcohol cues, which is suggestive of a conditioned craving response to the trauma memories (i.e., a history of drinking in response to trauma cues; Coffey et al., 2002). Related work has found that greater PTSD and AUD symptoms are associated with greater trauma and alcohol cue response in subclinical samples as well (Saladin et al., 2003). Follow-up studies demonstrated that trauma and alcohol cue-elicited craving decreases following imaginal exposure and PTSD/AUD treatment interventions (Coffey et al., 2006; Nosen et al., 2014).

Unfortunately, studies of trauma and substance cue reactivity are lacking with respect to other types of substances, precluding an ability to generalize these findings to non-AUD samples. However, it is likely that substance type does matter with respect to trauma cue reactivity, and thereby self-medication patterns of use; for example, in the only study to our knowledge to compare trauma cue–elicited craving as a function of substance type, Coffey and colleagues demonstrated that individuals with cocaine dependence exhibited significantly lower levels of trauma cue–elicited craving compared to individuals with alcohol dependence, in spite of similarities in vividness of trauma-related imagery (Coffey et al., 2002). Further investigations evaluating differences in trauma cue–elicited craving as a function of substance type may provide insight into potential differences in etiologies of various SUD comorbidities. The trauma and drug cue reactivity literature is also limited by a lack of longitudinal research in preclinical samples, which would provide greater insight into the etiological, versus the maintenance, role of self-medication in PTSD/SUD.

Treatment-Outcome Research

Treatment-outcome studies have been an important source of information for understanding PTSD/SUD associations. The literature is clear that individuals in treatment for SUD who have a PTSD diagnosis are significantly less likely to experience successful recovery, typically defined as abstinence (e.g., Brown, Stout, and Mueller, 1999). Therefore, the field has converged with respect to the identified need for concurrent, rather than sequential PTSD/SUD treatment (Berenz & Coffey, 2012; Mills et al., 2016). A number of treatment-outcome studies have evaluated the utility of administering prolonged exposure therapy, one of the most well validated treatments for PTSD (Resick, Williams, Suvak, Monson, & Gradus, 2012), concurrent with SUD treatment (Coffey et al., 2016; Persson et al., 2017; Zandberg et al., 2016). These studies have demonstrated success in treating PTSD within the context of addiction treatment settings, with a meta-analysis finding support for trauma-focused treatments in reducing PTSD symptoms when delivered concurrent with SUD treatment (Roberts, Roberts, Jones, & Bisson, 2015); however, the expected advantages of concurrent treatment in terms of abstinence rates have not been observed. Specifically, these studies have not demonstrated that successful treatment of PTSD leads to improvements in SUD outcomes that are above and beyond improvements seen with

SUD treatment alone, a finding that is inconsistent with the self-medication model of PTSD/SUD that led to concurrent treatment efforts in the first place. Although it cannot be concluded from this work that self-medication did not play a role in the etiology of individuals' PTSD/SUD, it does not appear that treating PTSD leads to superior SUD treatment outcomes compared to SUD treatment alone. However, it is important to acknowledge that concurrent PTSD treatment does not *worsen* SUD outcomes; rather, concurrent treatment leads to significant reductions in SUD outcomes that are comparable to reductions observed with SUD-only treatments, suggesting that PTSD may be safely and effectively treated at the same time as the SUD is treated, without jeopardizing SUD outcomes and with efficiently reducing the severity of both disorders. A likely conclusion is that while self-medication pathways are important for understanding PTSD/SUD, other risk and maintenance factors are also at play and need to be incorporated into etiological models and treatment packages.

Susceptibility Models

Susceptibility models presume that substance use and SUD increase risk for trauma exposure and/or PTSD (e.g., Brady, Back, & Coffey, 2004). Some epidemiological research has identified a prospective association between substance use and problems and subsequent risk for PTSD, although support has not been documented to the same degree as that for self-medication models. Cottler and colleagues (1992) found that in the St Louis Epidemiologic Catchment Area data (N = 2,663), cocaine and/or opiate users were more than three times as likely, compared to non-using controls, to report one or more lifetime traumatic events, and they also were significantly more likely to meet criteria for a PTSD diagnosis. Further, they found that substance use preceded the age of onset of PTSD. Our group (Berenz et al., 2017) conducted an investigation of bidirectional associations between PTSD and alcohol dependence using data from the first two waves of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC; Grant & Dawson, 2006). We applied Cox Proportional hazards models with time-dependent covariates to a sample of more than 11,000 individuals with lifetime trauma exposure and alcohol use (i.e., one or more drinks over one's lifetime); these methods take into account age of onset data (i.e., temporal association between the two disorder onsets), which provides a more fine-tuned estimate compared to logistic regression alone. Here, we found evidence for significant bidirectional associations between PTSD and alcohol dependence. However, when examining patterns of association by sex, we found that for men, the association between PTSD onset and subsequent alcohol dependence onset (HR = 1.290) was stronger than the reverse association (HR = 1.110). For women, the effect sizes for both orders of onset were significantly greater than for men, but alcohol dependence was more strongly related to subsequent PTSD onset (HR = 1.503) than the reverse association (HR = 1.370; Berenz et al., 2017). This study highlights the importance of considering sex differences in etiology of PTSD/SUD, which are further explored later in this book.

Theoretical Explanations

Three primary theoretical models have been proposed to explain associations between SUD phenotypes and subsequent trauma and PTSD risk. First, a relatively large body of work has supported the notion that substance use and problems increase risk for PTSD by increasing the odds that an individual will experience trauma exposure, namely sexual assault (e.g., Kaysen et al., 2006); see Figure 2.2. A number of studies in community and other trauma-exposed samples have also demonstrated increased risk for trauma exposure as a function of substance use and associated problems. For example, longitudinal data from the National Women's Study found that drug use, but not alcohol use, predicted future risk of a new assault (Kilpatrick et al., 1997). Similar findings have been documented in college student samples using longitudinal data (Kaysen et al., 2006). Further, Messman-Moore, Ward, and Brown found that substance use mediated an association between PTSD and sexual assault re-victimization (2009).

Second, it has been suggested that SUD phenotypes increase PTSD symptoms due to experiences of withdrawal heightening general affective distress and related symptoms, which affects not only PTSD but a range of psychiatric disorders (Schuckit et al., 1997). Most studies of SUD do not explicitly evaluate the role of withdrawal symptoms in SUD/PTSD associations but rely on peripheral indicators. For example, Durai and colleagues (2011) evaluated a sample of over 17,000 US male veterans in primary care at Veterans Affairs sites and found that "at-risk" drinking (defined as 14 or more drinks/week for men or 12 or more drinks/week for women; or 4 or more binge episodes in the past 3 months) was significantly associated with partial and full PTSD, as well as all PTSD symptom clusters. Other treatment studies have found that successful remission of SUD is associated with improvements in PTSD, even if PTSD symptoms are not directly addressed in treatment (Coffey et al., 2007). Further evaluation of these associations among individuals in acute withdrawal would be informative.

A third, less developed line of work, consisting largely of basic laboratory and animal studies, suggests that substance use, particularly use occurring during adolescence,

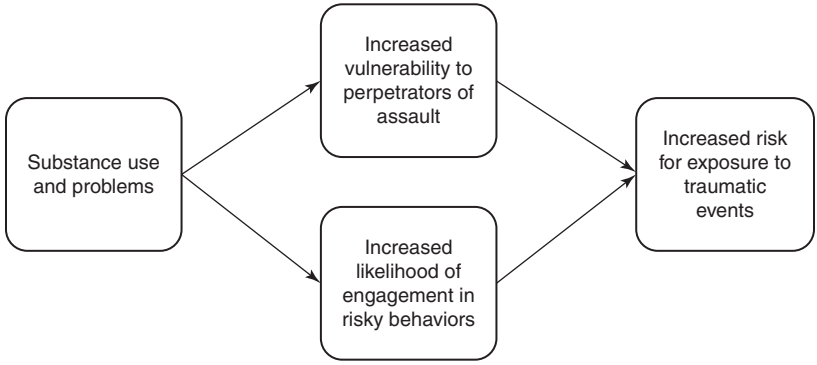

Figure 2.2 Theoretical illustration of how substance use could lead to increased risk for PTSD by way of heightened exposure to trauma.

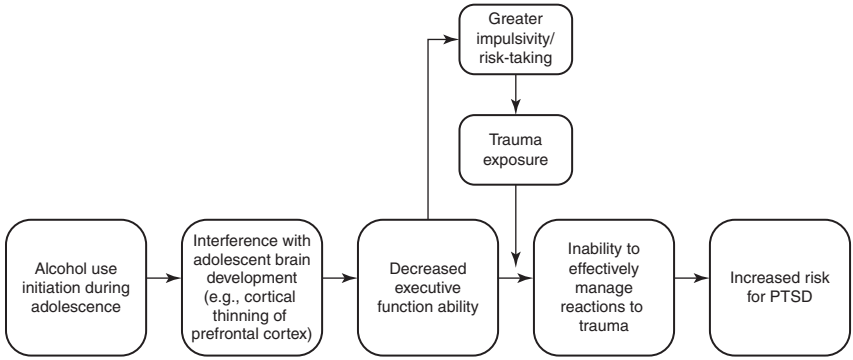

Figure 2.3 Theoretical model illustrating the potential role of adolescent alcohol use on risk for later-onset of PTSD symptoms.

increases risk for trauma exposure and/or PTSD through the damaging effects of substance use on regions of the brain critical for executive function, such as the prefrontal cortex (Guerri & Pascual, 2010); see Figure 2.3. A few investigations of adolescent substance use predicting adult PTSD symptoms have been conducted. For example, in an investigation using the Harlem Longitudinal Development Study, Lee and colleagues identified significant associations between chronic cannabis use in adolescence and onset of PTSD in adulthood (Lee, Brook, Finch, & Brook, 2018). Cross-sectional data among college students with a history of physical or sexual assault indicate that age of initiation of alcohol use during adolescence is significantly associated with PTSD symptom severity in young adulthood (Berenz et al., manuscript under review). Available evidence on related phenotypes indicates that adolescent alcohol use is associated with deficits on a range of neurodevelopmental outcomes relevant to the experience and management of negative affective states, such as reward learning (see Guerri & Pascual, 2010 for a review), impulsivity, and risk preference (McMurray, Amodeo, & Roitman, 2016; Sanchez-Roige, Pena-Oliver, Ripley, & Stephens, 2014; White et al., 2011). Such impairments could theoretically both increase risk for trauma exposure, by amplifying risk-taking and impulsive behavior, as well as increase risk for PTSD following exposure to trauma, by damaging one's ability to effectively regulate affective states and associated behavior.

Further research is needed to be able to evaluate whether and how adolescent alcohol and substance use impacts developmental trajectories in the context of trauma and PTSD risk. In fact, the National Institutes of Health (NIH) have funded two large, multi-site investigations geared toward understanding how alcohol impacts adolescent development, from a variety of methodological perspectives. First, the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) is an NIH-funded, multi-site effort founded in 2012 to evaluate the effects of adolescent alcohol use on developmental trajectories, utilizing state-of-the-art neuropsychological assessments, imaging data, and clinical measures (see Brown et al., 2015 for

more information). Second, the Adolescent Brain Cognitive Development (ABCD) Study is a multi-institute, multi-site consortium dedicated to evaluating a range of adolescent exposures, including substance use, in relation to adolescent and young adult development and similarly incorporates multi-method, intensive data collection methods in a large sample of youth (Jernigan, Brown, & ABCD Consortium Coordinators, 2018). Together, data resulting from these enormous efforts will undoubtedly shed light on potential mechanisms underlying PTSD/SUD comorbidity from multiple perspectives.

Summary and Future Directions

As described in this chapter, it is clear that the influences contributing to PTSD/SUD etiology and maintenance are varied, and there is no single pathway to developing these disorders. A number of conclusions may be drawn from the available literature to date. First, regardless of order of onset and etiology, it is clear that PTSD and SUD affect and maintain one another once they are both present. It may be the case that the factors responsible for the onset of this comorbidity do not entirely overlap with the factors maintaining it. This concept is well illustrated by the treatment-outcome data emerging from recent PTSD/SUD clinical trials, described earlier in this chapter, whereby successful PTSD outcomes from prolonged exposure interventions are not substantially improving abstinence rates post-discharge from treatment facilities, beyond abstinence rates that are observed with SUD-only treatment. Regardless, given that evidence-based PTSD treatment is safe and effective during SUD treatment, concurrent approaches should still be pursued to optimize overall gains to individuals' mental health and quality of life. However, further study is needed to understand *why* concurrent PTSD treatment is not improving SUD gains more than SUD-only treatments. Longitudinal research incorporating multi-method approaches, broadly speaking, also will be invaluable in elucidating the onset and trajectories of these debilitating conditions, both in preclinical and clinical samples.

Second, given the number of supported theoretical models for PTSD/SUD development, additional efforts at PTSD/SUD classification systems may be warranted. For example, it is possible that some individuals with PTSD/SUD fit more of a self-medication or internalizing/avoidance profile, whereas others are vulnerable as a function of familial or environmental risk for externalizing behaviors and symptoms. Large, longitudinal datasets such as those described previously will allow for exciting possibilities in terms of clustering individuals based not only on symptoms but on patterns of risk.

Third, efforts to contextualize studies of PTSD/SUD risk within a developmental framework are needed. Specifically, investigators would benefit from collaborating with developmental psychologists and physicians who treat adolescents to provide unique insights into various social-emotional-biological stages of development that could influence risk (e.g., pubertal stage). Much of the research evaluating the impact of adolescent alcohol use on cognitive development has been conducted in animals, or in non-trauma-exposed adolescents. An important step needed is evaluating whether disruptions to normal brain development, caused by exposure to alcohol during key

periods of adolescence, actually lead to greater risk for psychiatric symptoms, such as PTSD. Taken together, it is clear from the extant literature that PTSD/SUD development is highly complex. Further efforts to integrate the models highlighted here, as well as new models that may emerge, will yield the best results for the ultimate goal of enhancing prevention and treatment efforts in this high need population.

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